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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,522	02/11/2002	Cristian L. Achim	214001-00823-1	5288

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	6

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,522	ACHIM ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *3,7-13,16 and 18-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 5, 6, 14, 15, and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with **traverse** of Group I (claims 1, 2, 4, 5, 6, 14, 15, and 17) drawn to a method for treating a neurodegenerative illness in a patient with the election of FK506 in Paper No. 7 (18 January 2003) is acknowledged. The traversal is on the ground(s) that search of all the pending claims does not present a search burden on the Examiner. This is not found persuasive because the pending claims (1-28) in total represent 9 distinct and independent Inventions as set forth in Paper No. 6 (19 December 2002). Search of all the claims itself represents the undertaking of a search and then examination of all 9 Inventions, which presents an undue search burden on the Examiner. The species election requirement as set forth at pp. 5-6 ¶5-7 in Paper No. 7 (18 January 2003) is hereby *withdrawn.* Claims 3, 7-13, 16, and 18-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. Claims 1, 2, 4, 5, 6, 14, 15, and 17 are under examination.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Specification

5. The disclosure is objected to because of the following informalities: unnecessary period "50 ng./ml" (pp. 10 lines 6 and 13); misspelled "wk", should be "week" (pp. 15 line 21). Appropriate correction is required.

Claim Rejections - 35 USC § 112

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The following is a quotation of the second paragraph of 35 U.S.C. 112:
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims **1, 2, 4, 5, 6, 14, 15,** and **17** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for treating a neurodegenerative illness in a patient comprising culturing neuronal cells in vitro with an effective amount of FK506, V-10,367, or cyclosporin A; and transplanting said cultured neuronal cells into said*

patient wherein the neurodegenerative illness is Parkinson's disease, Huntington's disease, or ischemic cerebral stroke, does not reasonably provide enablement for *compounds having an affinity for immunophilins (other than FK506, V-10,367, or cyclosporin A), rapamycin, FK520, FK-523, 15-O-DeMe-FK-520, (4R)-[(E)-L-butenyl]-4,N-dimethyl-L-theronin, GPI-1046, or biological equivalents thereof or other neurodegenerative illnesses.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. The above invention is drawn to methods of treating a neurodegenerative illness in a patient comprising culturing second trimester human fetal neuronal cells *in vitro* with compounds having an affinity for immunophilins such as FK506 and transplanting said cells into a patient to who is administered compounds having an affinity for immunophilins such as FK506 during the transplantation procedure. The scopes of the claims are drawn to a method of treating a patient having a condition associated with neurodegeneration, wherein said treated cells are administered to patients such that the neurodegenerative illness is abated or otherwise relieved to a certain degree, wherein said condition may be a neurodegenerative illness including Parkinson's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Huntington's disease, acute brain degeneration associated with stroke, or other neurodegenerative diseases of the central nervous system that are candidates for treatment with tissue grafts of neuronal cells. The language of said claims encompasses a wide range of conditions.

8. The specification teaches a method of culturing second trimester human fetal cells *in vitro* and enriching the culture with FK506. The specification also teaches that said cells can be successfully transplanted into the striatum of a mouse (Example 2). However, the specification

as filed does not provide any guidance or examples that would enable a skilled artisan to use methods of using said cells in all neurodegenerative diseases or other compounds besides FK506 to enrich the second trimester human fetal cell culture. Additionally, a person skilled in the art would recognize that predicting the efficacy of a compound *in vivo* based solely on its performance of a single species (FK506) *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed compounds *in vivo* or in methods of treatment, such a disclosure would not be considered enabling since the state of neurodegenerative illness is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

9. The following references are cited herein to illustrate the state of the art of neurodegenerative illness treatment.

10. Concerning the breadth of the claims and the nature of the invention, Fricker-Gates et al. (2001) "Neural Transplantation: Restoring Complex Circuitry in the Striatum." Restrorative Neurology and Neuroscience 19(2-3): 119-138 teaches that numerous factors must be taken into consideration for cell transplantation procedures to be effective including but not limited to the source of the cell transplant material, the developmental stage (embryonic, fetal, or adult stem cell), agents used to enrich the cell transplant culture, the location of the cell tranplantation,

agents used to ensure or enhance survival of the cell transplant material (pp. 120-123; "**2. Prmary striatal tissue grafts**"). Thus the cell transplantation art is complex and contains a degree of uncertaininty for the skilled artisan to practice the claimed invention. Ficker-Gates et al. (2001) also discusses the difficulties of predicting successful treatment of cell transplantation (pp. 123-128; "**3. Are striatal transplants truly functional?**").

11. Concerning the nature of the invention, Wright et al. (September 1999) "A comparison of the sensitivity of pig and human peripheral blood mononuclear cells to the antiproliferative effects of traditional and newer immunosuppressive agents." Transplant Immunology 7(3): 141-147 teaches that immunosuppressants including but not limited to cyclosporin A, FK506, and rapamycin differ in their effects on porcine and human blood culture and are effective at different concentrations (Figures 1-7; Table 1; pp. 147). Therefore, a skilled artisan is confronted with undue experimentation to determine the efficacy and dosages necessary to practice the claimed invention to its full scope including "biological equivalents" of the immunophilin ligands, especially if administered to a patient.

12. Obstacles not withstanding, it is noted by the Examiner that cell transplantation therapy has successfully be practiced with patients suffering from Parkinson's disease (PD), Huntington's disease (HD), and stroke wherein the stroke resulted in acute cerebral damage. For instance, Sladek et al. (1998) "Intrastriatal Grafts from Multiple Donors Do Not Result in a Proportional Increase in Survival of Dopamine Neurons in Nonhuman Primates." Cell Transplantation 7(2): 87-96 (**IDS**) teaches the successful transplantation of cells into the striatum of MPTP-treated monkeys (an art accepted model of Parkinson's disease). Sladek et al. (1997) also discuss the problems of too few neurons per transplant, a problem addressed by the instant

application via the FK506 treatment. Further Savitz et al. (January-March 2003) "Cell Transplants Offer Promise for Stroke Recovery." The Journal of cardiovascular Nursing 18(1): 57-61 teaches the use of cell transplants to treat cerebral ischemic stroke (Table 1).

13. However, the Examiner maintains that the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of using compounds other than FK506, V-10,367, or cyclosporin A, or successfully treating neurodegernative illness besides, Parkinson's disease, Huntington's disease or stroke, as exemplified in the references above.

14. Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the transplantation of the second trimester human fetal cells into the striatum as being correlative or representative of the successful *in vivo* use of treatment of any and/or all diseases associated with neurodegeneration. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of treating any conditions or disease suspected of being associated with a particular neuronal population to be replaced. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* treatment effects provided by second trimester human fetal cells administered, and specifically regarding the instant methods claimed.

15. Said claims are drawn very broadly to methods of treating any condition or disease suspected of being associated with neurodegeneration in humans. Since the specification fails to provide any guidance for the successful treatment of such a broad range of diseases, and since resolution of the various complications in regards to using cell transplantation is highly

unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with acceptable toxicity and alleviation of symptoms that are successfully delivered to patients with PD, HD, or stroke. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

16. Claims 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 5 and 6 recite the use of an immunophilin ligand but do not give any concentrations as to allow for practice of the invention.

17. Claims 2 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2 and 15 recite the administration of an immunophilin ligand to a patient but do not give any dosages as to allow for practice of the invention.

18. Claims **5** and **6** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the limitation "biological equivalents thereof" but the metes and bounds of what an appropriate biological equivalent is not clear from the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims **1, 2, 4, 5, 6, 14, 15,** and **17** are rejected under 35 U.S.C. 103(a) as being unpatentable over **US 6140116** (31 October 2000) Dinsmore further in view of White et al. (January-February 1999) "Neuron-Enriched Second Trimester Human Cultures: Growth Factor Response and In Vivo Graft Survival." Cell Transplantation **8**(1): 59-73 and Costantini et al. (1998) "A Novel Immunophilin Ligand: Distinct Branching Effects on Dopamingeric Neurons in Culture and Neurotrophic Actions after Oral Administration in an Animal Model of Parkinson's Disease." Neurobiology of Disease **5**: 97-106 (**IDS**).

20. US 6140116 teaches a method of transplanting fetal porcine mesencephalic cells into the anterior putamen and posterior putamen to treat Parkinson's disease (Col. 74-77). US 6140116 also teaches the administration of an immunsuppressant agent such as cyclosporine (Col. 76 lines 17-28; equivalent to cyclosporine A and FK506 see Col. 4 lines 35-42). Concerning "neurodegenerative illness", US 6140116 teaches that the method can be used to treat neurodegeneration in the cortex and basal ganglia including by not limited to stroke and

Huntington's disease (Col. 5 lines 43-64; Col. 6 lines 18-28). US 6140116 also teaches the pretreatment of porcine mesencephalic cells with cyclosporine A or FK506 before transplantation (Figure 15A,B; Col. 21 lines 45-62) and the administration of cyclosporine A to patients before, during, or after transplantation (Figure 17A-17H; Col. 22 lines 12-67).

21. US 6140116 does not teach however, (a) the use of second trimester human fetal brain cells or (b) the pretreatment of the second trimester brain cells with V-10,367 prior to transplantation.

22. White et al. (1999) teaches that second trimester human fetal brain cells are good candidates for cell transplantation therapy for Parkinson's disease, a form of neurodegenerative illness (pp. 59 and 71).

23. Constantini et al. (1998) teaches the *in vitro* treatment of cultures of primary dopaminergic neurons with FK506 and V-10,367 increases neurite outgrowth and neuronal survival of TH+ neurons (Figure1). Constantini et al. (1998) teaches the V-10,367 is more potent than FK506 (Figure 1; pp. 99). Constantini et al. (1998) also teaches the oral administration of FK506 and V-10,367 as salubrious for an animal model of Parkinson's disease (Figure 2).

24. It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to use second trimester human fetal brain cells of White et al. (1999), pre-treat them with FK506 and V-10,367 as taught by Constantini et al. (1998) in the cell transplantation therapy as taught by US 6140116.

25. A person of ordinary skill in the art at the time the invention was made would have been motivated to use FK506 or V-10, 367 pretreated second trimester human fetal cells in the method of US 6140116 because of the advantages taught by White et al. (1998) concerning second

trimester human fetal cell (pp. 60; 67-69) such as ease of manipulation and better survival post-transplant and the therapeutic effects of FK506 and 10,367 in a PD model as shown by Constantini et al. (1998) (pp. 105). Further US 6140116 teaches that xenotransplants (cross species cell transplantation procedures) can result in the transmission of a pathogenic organism (Col. 4 lines 40-45; Col. 17 lines 22-54); use of human fetal cells would avoid this problem.

26. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because White et al. (1999) practices cell transplantation in SCID mice thereby demonstrating its use (pp. 67-69) and Constantini et al. (1998) demonstrated therapeutic effects of the administration of FK506 and V-10,367 in a PD model (pp.103; Figure 2). Thus the invention as a whole was *prima facia* obvious over the prior art.

Summary

27. Claims 1, 2, 4, 5, 6, 14, 15, and 17 are hereby rejected.

28. The following is a reference found by the Examiner during the art search for the instant application which is not prior art by nevertheless is of note:

a. US 2002/0110546 A1 (15 August 2002) Major et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
April 23, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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